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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,432	11/10/2003	Wojtek Auerbach	REG 784	4884

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REGENERON PHARMACEUTICALS, INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591

EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,432	AUERBACH ET AL.	
	Examiner	Art Unit	
	DAVID MONTANARI	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on 4/1/2008 have been entered.

2. Claims 25, 27 and 28 are amended.

3. Claims 1-24 and 29-32 are cancelled.

4. The declaration by Dr. Frendewey has been considered

5. The 35 USC 103(a) rejection has been withdrawn.

6. Claims 25-28 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining targeting frequency of a targeting construct in mouse embryonic stem (ES) cells, comprising:

(a) constructing a first targeting vector directed to a specific chromosomal location in a mouse ES cell, wherein the first targeting vector comprises a drug resistance gene operably linked to a, PGK promoter;

(b) introducing the first targeting vector into mouse ES cells *in vitro* to obtain a first group of targeted mouse ES cells;

(c) determining the number of targeted mouse ES cells in a cell colony as measured by targeted gene modifications due to targeted, non-random insertions of the first targeting vector in the first group of targeted mouse ES cells;

(d) constructing a second targeting vector directed to the specific chromosomal location of step (a), wherein the second targeting vector comprises a drug resistance gene operably linked to aubiquitin promoter;

(e) introducing the second targeting vector into a second group of mouse ES cells *in vitro* to obtain a second group of targeted mouse ES cells; and,

(f) determining a second number of targeted mouse ES cells in a cell colony as measured by targeted gene modifications due to targeted, non-random insertions of the second targeting vector in the second group of targeted mouse ES cells, wherein the second targeting number is at least two-fold higher than the first targeting number does not reasonably provide enablement for a method of determining targeting frequency of a targeting construct in mouse embryonic stem (ES) cells, comprising determining and comparing targeting efficiency. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a method which does not increase targeting frequency of a targeting construct.

Whereas the nature of the invention is method of comparing two different promoters (PGK and ubiquitin) ability to target a specific chromosomal location the recent amendments to claim 25 raises issues of enablement. Specifically claim 25 recites in steps (c) and (f) "determining a (sic) targeting efficiency as measured by targeted gene modifications due to targeted, non-random insertions of the (sic) targeting vector in a group of targeted mouse ES cells". However the instant specification does not disclose, nor teach the skilled artisan how efficiency is being determined in the claimed method. Efficiency is a comparison not a raw number. Based upon this lack of teaching in the specification efficiency could be the number of targeted ES cells per X and it not disclosed what is being compared to determine targeting efficiency. The art defines efficiency as a ratio, specifically "The ratio of the effective or useful output to the total input in any system" (The American Heritage Dictionary, Fourth Ed.). The

instant specification mentions the word efficiency four times, but provides no mention of how it is determined within the scope of the claimed method. Steps c and f of claim 25 only have one operable step and the practice of either step c or f will not determine efficiency, and if efficiency cannot be determined, then no comparison can be accomplished that will satisfy the requirements of step f, which is a comparison between the values obtained in steps c and f.

The working example provided in the instant specification at page 10 (see example 1) teaches that using the ubiquitin promoter to drive drug resistance gene expression was compared to the PGK promoters ability to drive expression of the same drug resistance gene in ES cell colonies. The example continues to teach that there was a 4-fold increase in targeting efficiency when using the ubiquitin promoter compared to the PGK promoter (pg. 10 parag. 0043). While there is an increase in targeting using the ubiquitin promoter in ES cells compared to the PGK promoter, the specification does not teach that this is an increase in efficiency. The specification does not teach what measurement the ubiquitin promoter is more efficient at compared to the PGK promoter. The increase in efficiency may include that the ubiquitin promoter targets more nucleotide regions compared to the PGK promoter or that the ubiquitin promoter require less energy to function or less starting material to achieve the targeting that is does compared to the PGK promoter. However, any comparisons between the ubiquitin and PGK promoters regarding efficiency would be up to the skilled artisan to interpret. This lack of teaching or guidance in the specification coupled with the teaching of how efficiency is defined and determined would lead the skilled artisan to the conclusion that the instantly claimed method cannot be practiced as written and thus non-enabled. It appears from a reading of Example 1 and the corresponding table on the page 11 of the specification that Applicant is ultimately relying on the "%

Targeting" in column 8 in Table 2 to determine that the ubiquitin promoter achieves a greater percentage of targeted mouse ES cells compared to the PGK promoter by measuring drug resistance. However, this again is not efficiency but rather just an increase in targeting to a specific chromosomal location of one construct as compared to another. Neither the specification nor Applicant's arguments regarding the instant amendment teach how the skilled artisan would measure efficiency with respect to targeting and contrasting two different promoter constructs driving a drug resistance gene in mouse ES cells. In summary, if efficiency cannot be determined to satisfy steps c and f of claim 25, then it cannot be contrasted as required by step f of claim 25, and thus targeting efficiency will not be determined to observe an increase in targeting frequency. The scope of the pending claim method has been written to better reflect what Applicants has taught and demonstrated the invention to be through an examination of their working example and data provided in Table 2.

Thus for the reasons above the claimed invention is not enabled for its entire scope and is therefore limited to the invention recited in the scope of enablement above.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID MONTANARI whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David A. Montanari, Ph.D.
AU 1632

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632